PATENT SPECIFICATION (11) 1 440 722

1 440 722

(21) Application No. 30176/74 (22) Filed 8 July 1974
(31) Convention Application No. 379 022
(32) Filed 13 July 1973
(31) Convention Application No. 465 381
(32) Filed 29 April 1974 in
(33) United States of America (US)
(44) Complete Specification published 23 June 1976
(51) INT CL² C07D 403/04
(52) Index at acceptance
C2C 1341 1412 1626 1628 200 213 215 220 226 22Y 246 247 250 251 252 25Y 28X 30Y 311 313 314 31Y 321 322 326 32Y 332 334 337 339 340 343 34Y 351 352 355 35Y 360 361 364 365 366 367 368 36Y 373 37X 37Y 385 386 387 396 400 40Y 43X 464 511 51X 51Y 536 551 55X 614 616 617 620 621 623 624 625 627 628 62Y 635 652 658 65X 670 671 672 675 676 678 680 681 689 694 697 69Y 708 720 72Y 73Y 760 761 762 763 775 77Y 790 79Y BE KA LE MG ML NF NR QL SJ TP TR TY UJ UK WE YX ZB

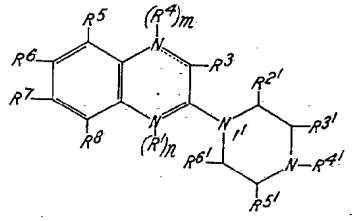
(72) Inventors EDWARD LOUIS ENGELHARDT, WILLIAM CARL LUMMA JR. and WALFRED SPENCER SAARI

(54) 2-(1'-PIPERAZINYL)-QUINOXALINE COMPOUNDS HAVING PHARMACEUTICAL ACTIVITY

(71) We, MERCK & CO INC, a corporation duly organised and existing under the laws of the State of New Jersey, United States of America, of Rahway, New Jersey, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention is concerned with 2-(1'-piperazinyl)-quinoxaline compounds.

The compounds that are the subject of the present invention are defined by the following structural formula:



I

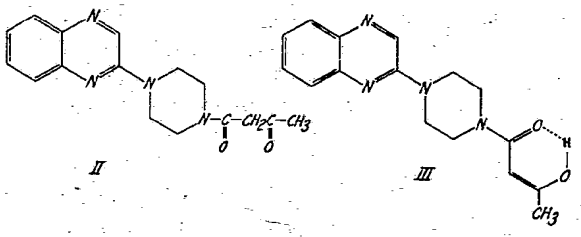
in which the dotted line indicates that the compounds are saturated or ethylenically unsaturated at the 3,4-positions; R^1 is oxygen; each of n and m is 0 or 1; R^4 is oxygen, hydrogen, alkyl, or aminoalkyl and R^3 is hydrogen, alkyl, alkoxycarbonyl, (e.g. methoxycarbonyl or ethoxycarbonyl), alkanoyl, aryl, substituted aryl, alkylthio, arylthio, alkoxy, amino, keto, alkylamino, dialkylamino, hydroxy, halo, carboxy, carbamoyl, N-alkylcarbamoyl, N,N-dialkylcarbamoyl or alkylimino; or R^4 and R^3 are joined to form, together with the adjacent nitrogen and carbon atoms of the quinoxaline nucleus, a 5-to-7-membered ring; each of R^5, R^6, R^7 and R^8 is hydrogen, allyl, haloalkyl, haloalkylthio, arylalkyl, cycloalkyl, aroyl, alkyl, nitro, alkanoyl, aryl, substituted aryl, alkylthio, alkylsulfonyl, haloalkylsulfonyl, alkylsulfinyl, haloalkylsulfinyl, arylthio, alkoxy, haloalkoxy, amino, alkylamino, dialkylamino, hydroxy, halo, carboxy, alkoxycarbonyl (e.g. ethoxycarbonyl or methoxycarbonyl), carbamoyl, N-alkylcarbamoyl, cyano, N,N-dialkyl-

carbamoyl or dialkylsulfamoyl; $R^{4'}$ is hydrogen, allyl, substituted allyl, haloalkyl, arylalkyl, cycloalkyl, alkanoyl, aroyl, alkylidenaminoxycarbonyl, alkoxycarbonylalkylenedithiocarbonyl, alkyldithiocarbonyl, β-cyanoethyl, alkoxycarbonyl, aryloxycarbonyl, or aralkyloxycarbonyl; and each of $R^{2'}$, $R^{3'}$, $R^{5'}$ and $R^{6'}$ is keto or two of the following univalent atoms or groups: hydrogen, alkyl, alkanoyl, aryl, substituted aryl, carboxy, alkoxycarbonyl, carbamoyl, N-alkylcarbamoyl or N,N-dialkylcarbamoyl, or $R^{2'}$ and $R^{3'}$ and/or $R^{5'}$ and $R^{6'}$ are joined to form a cycloaliphatic substituent sharing the 2',3'-carbon atoms and/or 5',6'-carbon atoms, as the case may be, of the piperazine ring.

Tests on compounds of the above formula have shown that they are useful as antidepressant agents and in the control of appetite, sleep and pain.

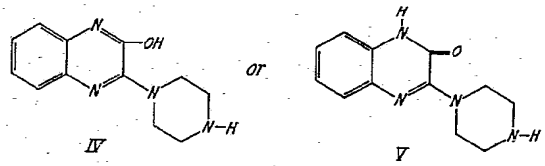
Also included within the scope of the present invention are non-toxic pharmaceutically acceptable salt, ester and amide derivative of I. Acid-addition salts are preferred. Such acid-addition salts of the piperazinylquinoxaline compounds are formed by mixing a solution of the piperazinylquinoxaline compound with a solution of a pharmaceutically acceptable non-toxic acid such as hydrochloric acid, fumaric acid, maleic acid, succinic acid, acetic acid, citric acid, tartaric acid, carbonic acid, sulfuric acid, phosphoric acid or nitric acid.

Also included within the scope of the present invention are isomeric and tautomeric forms of the compounds defined by the above structural formula. Thus, for example, 2-(4'-acetoacetyl-1'-piperazinyl)-quinoxaline exists in solution in two tautomeric forms, illustrated below:



II III

Likewise, for example, the compound 3-hydroxy-2-(1'-piperazinyl)-quinoxaline is primarily present as the 3-keto-4-(H)-tautomer, both forms of which are illustrated by the following structural formula:



IV or V

3-hydroxy form 3-keto-4-(H) form

One sub-group of antidepressant compounds represented by the above formula I, viz., those in which R^6 is hydrogen, are characterized by serotonin-like activity in the central nervous system. A particular member of this sub-group, R^3 = hydroxy (formula IV or V), is exceptionally notable for the long duration of serotonin-like activity following administration to a test animal. A second sub-group of antidepressant compounds represented by the above formula I, viz., those in which R^6 is other than hydrogen, are characterized by their ability to block the reuptake of serotonin and thus enhance the action of endogenous serotonin. Thus, both groups of compounds act through the central nervous system but have different modes of action relative to the response of the organism and to the action of 5-hydroxy-tryptamine, herein referred to as serotonin. It appears that compounds of the present invention may derive their utility in the management of depression from their activity in inhibiting the reuptake of serotonin at the nerve ending and thus potentiating or prolonging its action.

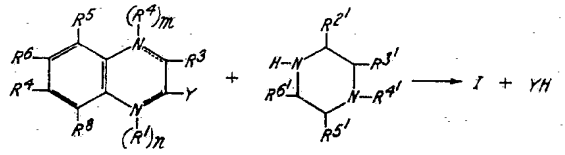
Preferred compounds of this invention are those in which n is 0; R^4 is hydrogen or alkyl; R^3 is hydrogen, hydroxyl, alkoxy, aryloxy, nitro, keto, amino, dialkylamino, alkanoyl, carboxyl or halo; R^5, R^6, R^7 and R^8 are hydrogen, halogen, alkoxy, hydroxyl, dialkylsulfamoyl, haloalkylthio, haloalkylsulfinyl, haloalkyl-

sulfonyl, haloalkoxy, cyano, alkyl, nitro, trifluoromethyl, or haloalkyl; $R^{4'}$ is hydrogen, benzyl, allyl, acetoacetyl alkoxycarbonyl, alkylidenaminoxycarbonyl, carboalkoxyalkylenedithiocarbonyl, or alkyldithiocarbonyl; $R^{2'}$, $R^{3'}$, $R^{5'}$ and $R^{6'}$ are hydrogen, keto, or alkyl; or $R^{2'}$ and $R^{3'}$ and/or $R^{5'}$ and $R^{6'}$ are joined, together with the carbon atoms to which they are attached, to form a cycloaliphatic substituent.

In the foregoing definitions, haloalkylthio may be trifluoromethylthio; haloalkylsulfinyl may be trifluoromethylsulfinyl, haloalkylsulfonyl may be trifluoromethylsulfonyl, and halo alkoxy may be trifluoromethoxy; and of the above-named substituents that are alkyl or that involve alkyl residues, those having from 1 to 5 carbon atoms in the alkyl group constitute a preferred class.

Particularly preferred are those compounds in which: R^3 is hydroxyl [or keto-4(H)form] or hydrogen; R^5 and R^8 are hydrogen, fluorine, bromine, chlorine, hydroxy, C_{1-5} alkoxy, or di(C_{1-5} alkyl)-sulfamoyl; R^6 is hydrogen, fluorine, bromine, chlorine, cyano, nitro or trifluoromethyl; $R^{3'}$ and $R^{5'}$ are hydrogen or keto; R^7, $R^{2'}$, and $R^{6'}$ are hydrogen; $R^{4'}$ is hydrogen or alkylidenaminoxycarbonyl having from 2 to 6 carbon atoms; and n is 0.

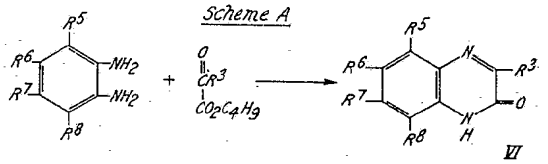
In accordance with the present invention, the compounds of Formula I are prepared by reacting, preferably in a liquid phase, a suitably substituted quinoxaline compound having a replaceable group, Y, such as alkylsulfinyl, alkylsulfonyl, halogen, mercapto, trialkylammonium, tosyloxy, mesyloxy, trialkylsilyoxy such as trimethylsilyloxy, amino, alkylamino, dialkylamino, trialkylammonium, alkoxy, or alkylthio at the 2-position and a suitably substituted piperazine compound. The following equation illustrates the preferred process.



where all substituents are as previously defined.

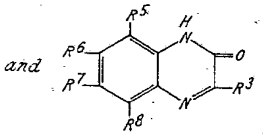
Many of the quinoxaline intermediate compounds are known and readily available. In the alternative all of the quinoxalines necessary for the preparation of the 2-piperazinylquinoxalines of the present invention may be prepared, for example, by one or more of the following general schemes where all substituents are as previously defined:

Scheme A



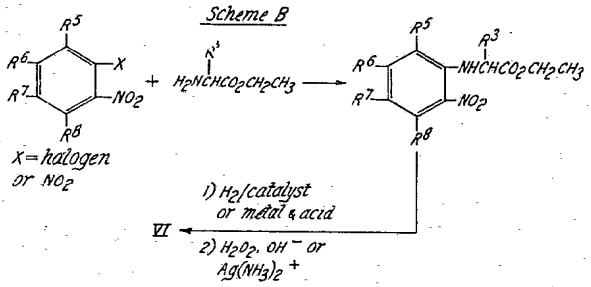
VI

and

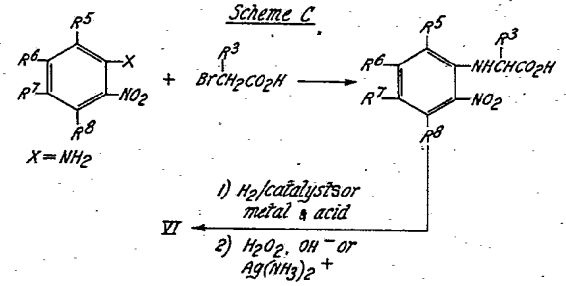


VII

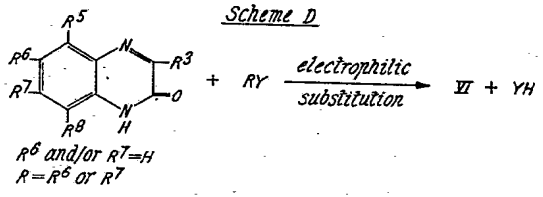
Scheme B



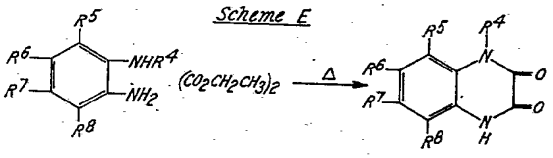
Scheme C



Scheme D



Scheme E



The isomers VI and VII may be separated by fractional crystallization and unambiguously identified by comparison with the corresponding product obtained by Schemes B or C. It is to be noted that these isomers are, depending upon the pattern of the nuclear substituents, each useful in the preparation of the piperazinylquinoxalines of the present invention. The needed 2Y-substituted quinoxalines are readily prepared by known procedures from the 2-keto-quinoxalines (prepared, for example, by any of Schemes A to E); for example, the 2-halo form is prepared by treating the 2-keto form with a halogenating agent. In the examples which follow, these and other schemes for the preparation of needed intermediate reactants are specifically, but representatively, demonstrated.

The 2Y-substituted quinoxaline and piperazine reactants are mixed with or without an added polar solvent and preferably heated until the reaction is essentially complete. The reaction mixture is then diluted with water and the product extracted with a water-immiscible solvent.

The solvent used as the reaction medium is preferably a polar solvent such as water, aqueous solvent mixtures, oxygenated solvents such as C_{1-5} alkanols, e.g. methanol, ethanol, *n*-propanol, isopropanol, or butyl alcohols, nitrogen-containing solvents such as N,N-di(C_{1-5} alkyl)amides as, for example, dimethylacetamide or dimethylformamide, and mixtures of such materials with water. The reaction can be conveniently conducted in the absence of an added solvent.

The reaction mixture is preferably heated to a temperature of from 0—200°C. or to the reflux temperature of the reaction medium for a period of from 15 minutes to 24 hours. A period of from 1—5 hours at a temperature of from 100—150°C. is particularly preferred.

Also included within the scope of the present invention is a process for producing the N-substituted derivatives of the 2-(1'-piperazinyl)-quinoxaline, i.e., the N-alkyl (N-ethyl, -methyl, -propyl), the N-alkenyl (N-allyl, -methallyl), the N-haloalkyl-(N-chloromethyl, N-trifluoromethyl), the N-aralkyl (N-benzyl, N-phenethyl), the N-cycloalkyl (N-cyclopentyl, N-cyclohexyl), the N-alkanoyl (N-acetyl, N-propionyl, N-acetoacetyl), the N-aroyl (N-benzoyl, N-toluyl), N-carboalkoxy (N-carbomethoxy, N-carboethoxy), N-β-hydroxyalkyl, N-alkylidenaminoxycarbonyl, N-carboalkoxyalkylenedithiocarbonyl, and N-alkyl-dithiocarbonyl. These derivatives are formed in accordance with the present

invention by reaction of the selected 2-(1'-piperazinyl)-quinoxaline compound of Formula I above where $R^{4'}$ is hydrogen with an ester, anhydride, alkyl halide, aralkyl halide, acyl halide or alkenyl halide, thus replacing the hydrogen of the piperazinyl nitrogen by the substituent derived from the reactant chosen.

When used in the treatment of depression in patients suffering from mental disorders involving depression, the dosage level of compounds of the present invention typically ranges from 0.1 to 500 mg./day, and preferably is from 0.1 to 100 mg./day.

When used in the control of appetite or pain, the dosage level of compounds of the present invention is preferably from 0.1—500 mg./day, divided into equal unit dosages of from 0.1—100 mg./dose.

The compounds of the invention are also useful in influencing sleep patterns in man in similar dose ranges.

Included within the scope of the present invention are pharmaceutical compositions comprising such piperazinylquinoxalines of Formula I. Preferably these compositions are in unit dosage forms such as tablets, pills, capsules, powders, granules, sterile parenteral solutions or suspensions. For preparing solid compositions such as tablets, the principal active ingredient is mixed with a pharmaceutical carrier, i.e., conventional tableting ingredients such as corn starch, lactose, sucrose, sorbitol, talc, stearic acid, magnesium stearate, dicalcium phosphate, gums, and other pharmaceutical diluents, e.g., water, to form a solid preformulation composition containing a homogeneous mixture of a piperazinylquinoxaline of the present invention, or a nontoxic pharmaceutically acceptable acid addition salt thereof. When referring to these preformulation compositions as homogeneous, it is meant that the active ingredient, i.e., the substituted piperazinylquinoxaline or salt thereof, is dispersed evenly throughout the composition so that the composition may be readily subdivided into equally effective unit dosage forms such as tablets, pills or capsules. This solid preformulation composition is then subdivided into unit dosage forms of the type described above containing from 0.1—100 mg. of the piperazinylquinoxaline compound or salt per unit dose.

The tablets or pills can be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action of the piperazinylquinoxaline compound or salt thereof. For example, the tablet or pill can comprise an inner dosage and outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer, which serves to resist disintegration in the stomach and permits the inner component to pass intact into duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids or mixtures of polymeric acids with such materials as shellac, shellac and cetyl alcohol or cellulose acetate.

The liquid forms in which the compositions of the present invention may be incorporated for administration include aqueous solutions, suitably flavored syrups, aqueous or oily suspensions, flavored emulsions with edible oils such as cottonseed oil, sesame oil, coconut oil or peanut oil, elixirs, and similar pharmaceutical vehicles.

The formulations of the piperazinylquinoxaline compound and a pharmaceutically acceptable salt are normally administered orally, parenterally, or rectally. Orally, they may be administered in tablets, capsules, suspensions or syrups, the preferred dosage form being a compressed tablet containing from 1—100 mg. of the active ingredient. The optimum quantities of the piperazinylquinoxaline or equivalent salt depend on the particular compound of salt employed and the particular type of clinical condition treated, oral dosage amounts of the preferred formulation are used in the range of 0.5—500 mg./day, especially in the range of 0.5—100 mg./day. For intravenous administration, the dose levels utilized include from 0.1—100 mg./day and preferably in the range of 0.1—20 mg./day of the selected piperazinylquinoxaline or equivalent salt. Within these noted ranges the dosage must of course be adjusted to the need of the patient, taking into account the particular clinical condition and other factors including general health, weight, and age of the patient. Ultimately these considerations are at the routine descretion of the therapist. The daily doses are expressed as mg. of the particular piperazinylquinoxaline compound per patient per day assuming a patient weight of from about 45—90 kg.

The following examples representatively illustrate, but do not limit, the products, processes and compositions of the present invention.

EXAMPLE 1.

Preparation of 3-keto-(4H)-2-(1'-piperazinyl)-quinoxaline

One mole of 2,3-dimethoxyquinoxaline and four (4.0) moles of anhydrous piperazine are heated with stirring under N_2 at a bath temperature of 130°C. until the mixture is melted and then at a bath temperature of 160°C. until 2.0 moles of methanol have distilled off. The mixture is cooled and diluted with ice water (1.0 l.) and benzene (1.0 l.). The mixture is stirred for several hours while warming to 25°C., the layers are separated, and the aqueous layer extracted with benzene. The combined benzene extracts are washed with water and the saturated aqueous layer extracted with benzene. The combined benzene extracts are washed with water and saturated aqueous NaCl and dried over Na_2SO_4. Evaporation of the filtered benzene solution to the cloud point and cooling gives the crude product, which is purified by repeated crystallization from benzene to give colorless needles of 3-keto-(4H)-2-(1'-piperazinyl)-quinoxaline m.p. 183.5—184.5°C.

EXAMPLE 1a.

6-Cyano-2(1'-piperazinyl)-quinoxaline

2,3-Dichloro-6-cyanoquinoxaline (4.48 g., 0.020 mole), N-formylpiperazine (2.28 g., 0.020 mole) and *bis* 1,8-(dimethylamino)naphthalene (4.29 g., 0.020 mole) are combined in 50 ml. dry acetonitrile at 0°C. The mixture is stirred for 6 hours at 0°C. and 16 hours at 25°C. The suspension is quenched into 100 ml. of ice water containing 5.0 ml. of concentrated hydrochloric acid and the yellow solid collected and washed with water to give, after recrystallization from acetonitrile, 3.20 g. of 2-(4'-formyl-1'-piperazinyl)-3-chloro-6-cyanoquinoxaline (m.p. 202—204°C.). 2.72 g. of this intermediate compound is hydrogenated at atmospheric pressure in 25.0 ml. ethylacetate in the presence of 1.39 ml. triethylamine and 0.50 g. of 10% palladium-on-charcoal catalyst for 10 hours. The resulting hydrogenation mixture is treated with 2.0 ml. of concentrated hydrochloric acid; the ethylacetate evaporated on the steam bath; the residue heated with 15.0 ml. of water at 90°C. for 1.0 hour; and the mixture filtered. The filtrate is basified with concentrated aqueous ammonia and extracted with chloroform, and the chloroform is dried over Na_2SO_4, filtered, and concentrated. The resulting 6-cyano-2(1'-piperazinyl)-quinoxaline is converted to its hydrochloride salt, which melts at 323—325°C., by the procedure of Example 2.

EXAMPLE 2.

Preparation of 2-(1'-piperazinyl)-quinoxaline; 6-chloro-2-(1'-piperazinyl)-quinoxaline; 6-cyano-2-(1'-piperazinyl)-quinoxaline; and 6-trifluoromethyl-2-(1'-piperazinyl)-quinoxaline

One (1.0) mole of 2-chloroquinoxaline; 2,6-dichloroquinoxaline; 2-chloro-6-cyanoquinoxaline; and 2-chloro-6-trifluoromethylquinoxaline, respectively, and 2.0 moles of piperazine are mixed in 1.0 liter of 2-butanol and the mixture refluxed for 6 hours under nitrogen, followed by removal of excess of solvent *in vacuo*. The residue is partitioned between 1.0 l. of 2*N* Na_2CO_3 and 1.0 l. of $CHCl_3$. The aqueous layer is re-extracted with 500 ml. $CHCl_3$, and the combined $CHCl_3$ extracts are dried over K_2CO_3, filtered and concentrated *in vacuo* to provide 2-(1'-piperazinyl)-quinoxaline; 6-chloro-2-(1'-piperazinyl)-quinoxaline; 6-cyano-2-(1'-piperazinyl)-quinoxaline; and 6-trifluoromethyl-2-(1'-piperazinyl)-quinoxaline, respectively.

The fumarate and hydrogen chloride salts of the above-prepared compounds are prepared respectively by the dropwise addition of a saturated ethanolic solution of the respective acid to a saturated ethanolic solution of the respective piperazinyl-quinoxaline; the respective salt precipitate is collected, recrystallized from ethanol and dried.

EXAMPLE 3.

Following substantially the procedure of Example 2, the representative piperazinylquinoxalines of the present invention set forth in Table I are prepared. In Table I, the first column names the particular piperazinylquinoxaline product; the second column identifies the essential starting reactants; the third column gives characterizing remarks or data such as melting point, specific salts, and specific exceptions to the general procedure of Example 2. In the table, "P" symbolizes piperazine or piperazinyl and "Q" symbolizes quinoxaline.

TABLE I

Product	Reactants	Remarks
3-chloro-2-(1' P)-Q	P & 2,3-dichloro Q	.HCl salt, m.p. 246–247°C
3-chloro-2-(4' -methyl-1' -P)-Q	N-methyl P & 2,3-dichloro-Q	.HCl salt, m.p. 260–261°C. dec.
2-(4' -methyl-1' -P)-Q	N-methyl P & 2-chloro Q	.2HCl salt, m.p. 254–256°C. dec.
7-methoxy-2-(1' -P)-Q	P & 2-chloro-7-methoxy-Q	.2HCl salt, m.p. 258–259°C. dec.
7-nitro-2-(1' -P)-Q	P & 7-nitro-2-chloro-Q	.HCl salt, m.p. 305–306°C.
3-chloro-7-trifluoro-methyl-2-(1' -P)-Q	P & 2,3-dichloro-7-trifluoromethyl-Q	.HCl salt, m.p. 274–275°C.
3,6,7-trimethyl-2-(1' -P)-Q	P & 2-chloro-3,6,7-trimethyl-Q	m.p. 252–253°C.
2-(3' -carboxyl-1' -P)-Q	P-2-carboxylic acid & 2-chloro-Q	.2/9 acetate salt, m.p. 241–243°C.
2-(3' -keto-1' -P)-Q	2-keto P & 2-chloro-Q	.HCl.H_2O salt, m.p. 223–225°C.
6-nitro-2-(1' -P-)-Q	P & 2-chloro-6-nitro-Q	.HCl salt, m.p. 335–336°C. dec.
3-phenyl-2-(1' -P)-Q	P & 2-chloro-3-phenyl-Q	
3-ethoxycarbonyl-2-(1' -P)-Q	P & 2-chloro-3-ethoxy-carbonyl-Q	
6-bromo-2-(1' -P)-Q	P & 6-bromo-2-chloro-Q	
6-chloro-3-phenylthio-2-(1' -P)-Q	P & 2,6-dichloro-3-phenylthio-Q	.HCl salt, m.p. 276–277°C.
6-trifluoromethyl-3-phenylthio-2-(1' -P)-Q	P & 2-chloro-3-phenyl-thio-6-trifluoromethyl-Q	.HCl salt, m.p. 262–263°C.
6-Methylsulfonyl-3-chloro-2-(1' -P)-Q	P & 2,3-dichloro-6-methylsulfonyl-Q	.HCl salt, m.p. 315–316°C.
6-methylsulfonyl-2-(1' -P)-Q	P & 6-methylsulfonyl-2-chloro-Q	.Fumarate salt, m.p. 205–206°C.
6,7-dichloro-2-(1' -P)-Q	P & 2,6,7-trichloro-Q	.HCl salt, m.p. 347°C.
6-methyl-2-(1' -P)-Q	P & 2-chloro-6-methyl-Q	.Fumarate salt, m.p. 198–200°C.; .HCl salt, m.p. 280–283°C.
6-sulfamoyl-3-chloro-2-(4' -methyl-1' -P)-Q	N-methyl-P & 2,3-dichloro-6-sulfamoyl-Q	m.p. 202.5–204°C.
6-(N-2-hydroxyethylcarbamoyl)-3-chloro(4' -β-hydroxyethyl-1' -P)-Q	N-(2-hydroxyethyl)-P & 2,3-dichloro-6-(N-2-hydroxyethylcarbamoyl)-Q	.HCl salt, m.p. 230–240.5°C.
3-acetyl-2-(1' -P)-Q	P & 3-acetyl-2-chloro-Q	
5-nitro-2-(1' -P)-Q	P & 2-chloro-5-nitro-Q	.HCl salt, m.p. 309°C. dec.
6-bromo-2-(1' -P)-Q	P & 2-chloro-6-bromo-Q	.HCl salt, m.p. 312–314°C. dec.
2(1' -P)-Q-4-oxide	P & 2-chloro Q-4-oxide	.HCl salt, m.p. 242–243°C.

TABLE I (Continued)

Product	Reactants	Remarks
2-(1'-P)-Q-1-oxide	P & 2-chloro Q-1-oxide	.HCl.H_2O, m.p. 264–266°C.
7-chloro-5-nitro-2-(1'-P)-Q	P & 5-nitro-2,7-dichloro-Q	.HCl salt, m.p. 294–296°C.
6-hydroxy-2-(1'-P)-Q	P & 6-hydroxy-2-chloro-Q	.Acetate salt, m.p. 185–187°C.
5-chloro-2-(1'-P)-Q	P & 2,5-dichloro-Q	.HCl salt, m.p. 323–325°C. dec.
6-chloro-2-(4'-methyl-1'-P)-Q	N-methyl-P & 2,6-dichloro-Q	.HCl salt, m.p. 292–293°C. dec.
2-(1'-P)-3-keto-(4H)-4-methyl-Q	P & 2-chloro-3-keto-(4H)-4-methyl-Q	m.p. 80–82°C.
3-(2'-hydroxyethylamino)-2-(1'-P)-Q	P & 3-(2'-hydroxyethylamino)-2-chloro-Q	.2HCl-H_2O salt, m.p. 274–276°C.
4-(1'-P)-1,2-dihydroiminazo-[1,2a]-Q	P & 4-chloro-1,2-dihydroimidazo-[1,2a]-Q	.2HCl salt, m.p. 320–321°C.
3-amino-2-(1'-P)-Q	P & 3-amino-2-chloro-Q	.2HCl salt, m.p. 296–298°C. dec.
2-(1'-P)-5-fluoro-Q	P & 2-chloro-5-fluoro-Q	.Hydrogen fumarate, m.p. 209.5–210.5°C. dec.
8-fluoro-2-(1'-P)-Q	P & 2-chloro-8-fluoro-Q	.Fumarate salt, m.p. 215–218°C. dec.
6-methoxy-2-(1'-P)-Q	P & 2-chloro-6-methoxy-Q	.HCl salt, m.p. 300–301°C. dec.
6-chloro-2-(1'-P)-Q	P & 2,6-dichloro-Q	.HCl salt, m.p. 320–321°C. dec.
6-chloro-3-ethoxy-2-(1'-P)-Q	P & 2,6-dichloro-3-ethoxy-Q	.Fumarate salt, m.p. 187–188°C.
6-trifluoromethyl-2-(1'-P)-Q	P & 2-chloro-6-trifluoromethyl Q	.Fumarate salt, m.p. 220–221°C.
2-(4'-acetoacetyl-1'-P)-Q	2-(1'-P)-Q & diketene in ethylacetate	m.p. 133.5–134.5°C.
2-(4'-methoxycarbonyl-1'-P)-Q	2-(1'-P)-Q & p-nitrophenylmethylcarbonate in ethylacetate	m.p. 109–110°C.
2-(4'-acetyl-1'-P)-Q	2-(1'-P)-Q & acetic anhydride (excess)	m.p. 148.5–150°C.
6-chloro-2-(4'-acetyl-1'-P)-Q	6-chloro-2-(1'-P)-Q & acetic anhydride (excess)	m.p. 170–172°C.
6-chloro-2-(4'-isopropylidenaminocarbonyl-1'-P)-Q	6-chloro-2-(1'-P)-Q & isopropylidenaminocarbonyl chloride	m.p. 173–173.5°C.
6-chloro-2-(4'-benzyloxycarbonyl-1'-P)-Q	6-chloro-2-(1'-P)-Q & benzyloxycarbonyl chloride	m.p. 124.5–125.5°C.

TABLE I (Continued)

Product	Reactants	Remarks
6-chloro-2-(4'-carbethoxynethyldithiocarbonyl-1'-P)-Q	6-chloro-2-(1'-P)-Q & carbethoxymethyldithiocarbonyl chloride	m.p. 121°C., dec.
6-chloro-2-(4'-succinimidomethoxycarbonyl-1'-P)-Q	6-chloro-2-(1'-P)-Q & succinimidomethoxycarbonyl chloride	m.p. 168.5–169.5°C.
6-amino-2-(1'-P)-Q	6-nitro-2-(1'-P)-Q	Reduction achieved by hydrogenation in the presence of 10% palladium on charcoal catalyst
6-chloro-2-(4'-allyl-1'-P)-Q	6-chloro-2-(1'-P)-Q & allylchloride in acetonitrile at reflux	.HCl.H_2O salt m.p. 237–239°C.
6-chloro-2-(4'-*trans*-γ-chloroallyl-1'-P)-Q	6-chloro-2-(1'-P)-Q & *trans*-γ-chloroallyl-chloride in acetonitrile at reflux	.HCl salt, m.p. 234–235°C.
2(4'-methyl-1'-P)-3-keto(4H)-Q	2-(1'-P)-3-keto(4H)-Q & methyliodide in acetonitrile at reflux	.Acetate salt, m.p. 185–187°C.

The following Examples representatively illustrate preparation of the necessary reactants involved in Examples 1—3 and Table I.

EXAMPLE 4.

Preparation of 5- and 8-fluoro-2-keto-(1H)-quinoxaline

A solution of 3-fluoro-*o*-phenylenediamine (0.040 mole) is treated with n-butylglyoxalate (6.5 g., 0.050 mole) and 25 ml. water and the mixture refluxed for 3 hours under N_2. The mixture is cooled and filtered to give 7 g. of crude product.

The crude product is heated with 4.77 g. of Na_2CO_3 in 50 ml. water. The dark mixture is filtered through a pad of diatomaceous earth. The resulting filtrate is heated to 80°C, with 2.58 ml. of glacial acetic acid and again filtered to provide from the filtrate crude 5-fluoro isomer, which is purified by two recrystallizations from boiling tetrahydrofuran to provide tan plates of 5-fluoro-2-keto-(1H)-quinoxaline, m.p. 289.5°—291°C.

The mother liquors from the 5-fluoro isomer are adjusted to pH 6 with concentrated HCl to give 8-fluoro-2-keto-(1H)-quinoxaline, m.p. 255—256°C. after two recrystallizations from boiling isopropanol.

Where in Example 4, the 3-fluoro-*o*-phenylenediamine is replaced by an equivalent amount of 4-trifluoromethyl-*o*-phenylenediamine; 4,5-dichloro-*o*-phenylenediamine; 3-chloro-*o*-phenylenediamine; 3-nitro-*o*-phenylenediamine; and 3-nitro-5-chloro-*o*-phenylenediamine, respectively, there is obtained 6- and 7-trifluoromethyl-2-keto-(1H)-quinoxaline (the former melting at 118—120°C.); 6,7-dichloro-2-keto-(1H)-quinoxaline; 5- and 8-chloro-2-keto-(1H)-quinoxaline (the former melting at 313—315°C.); 5- and 8-nitro-2-keto-(1H)-quinoxaline (the former decomposing without melting); and 7-chloro-5-nitro-2- (and 3-) keto(1H and 4H)-quinoxaline (the first mentioned melting at 175—178°C.), respectively.

EXAMPLE 5.

Preparation of 8-fluoro-2-keto-(1H)-quinoxaline

2,6-Difluoronitrobenzene (7.0 g., 0.044 mole) is added to a solution of freshly prepared glycine ethylester base (obtained by dissolving 15 g., 0.11 mole of the hydrochloride in 0.1 *M* aqueous NaOH and extracting with benzene at 0°) in 150 ml. dry benzene. The resulting mixture is refluxed 20 hours under N_2, cooled to 20°C., and washed with three 50 ml. volumes of water. The benzene layer is concentrated *in vacuo* and the residue recrystallized from *n*-butyl chloride to give 2.30 g. of 3-fluoro-2-nitroanilinoacetic acid ethyl ester, m.p. 61—63°C.

To a gently stirred solution of 3-fluoro-2-nitroanilinoacetic acid ethyl ester (2.02 g., 0.00835 mole) in 13 ml. absolute ethanol is added 4.0 g. of mossy tin followed by 8.3 ml. of 12*M* hydrochloric acid. The resulting exothermic reaction mixture is stirred for 40 minutes and then heated for 15 minutes at 90°C., and the resulting nearly colorless solution is filtered through glass wool. The filtrate is treated with H_2S until copious flocculation of SnS is observed and thereafter the dark suspension is heated at 90°C. and filtered.

The cooled filtrate is refiltered to give a white solid which is treated with 19 ml. of aqueous 8.0 wt. % sodium hydroxide and 1.7 ml. of 30% hydrogen peroxide. The resulting exothermic reaction mixture is stirred for 10 minutes, heated for 5 minutes at 90°C., and filtered. Acidification of the filtrate with glacial acetic acid gives crude 8-fluoro-2-keto-(1H)-quinoxaline which, after recrystallization from isopropanol, melts at 208—210°C.

Following the procedure exactly as described in Example 5 except that the 2,6-difluoronitrobenzene of Example 5 is replaced by equivalent amounts of 2,3-, 2,5-, and 2,4-difluoronitrobenzene, respectively, there are obtained 5-fluoro-2-keto-(1H)-quinoxaline, 7-fluoro-2-keto-(1H)-quinoxaline, and 6-fluoro-2-keto-(1H)-quinoxaline (m.p. 300—302°C.), respectively; and similarly when 2-fluoro-4-hydroxynitrobenzene and 2-fluoro-4-cyanonitrobenzene, respectively, replace 2,6-difluoronitrobenzene there are obtained 6-hydroxy-2-keto-(1H)-quinoxaline and 6-cyano-2-keto-(1H)-quinoxaline, respectively.

EXAMPLE 6.

Preparation of 6-(methylsulfonyl)-2-keto-(1H)-quinoxaline

5-Fluoro-2-nitroanilinoacetic acid ethyl ester (12.11 g., 0.050 mole, melting point, 116—117°C.), prepared as in Example 5 when the 2,6-difluoronitrobenzene of Example 5 is replaced by an equivalent amount of 2,4-difluoronitrobenzene, is reacted with 100 ml. of a solution of sodium methylmercaptide (obtained by bubbling CH_3SH through 100 ml. of ethanol containing 1.2 g. sodium metal) for 1 hour at 25°C. The precipitated product is recrystallized from *n*-butychloride to provide 5-(methylthio)-2-nitroanilinoacetic acid ethyl ester, which melts at 79—81°C. This product (12.2 g., 0.0452 mole) is oxidized with 15 ml. 30% hydrogen peroxide in 100 ml. glacial acetic acid at 60°C. and the resulting mixture poured into 100 ml. ice water to give 5-(methylsulfonyl)-2-nitroanilinoacetic acid ethyl ester, which melts after recrystallization from benzene at 156—157°C. This latter product (10.8 g.) is reduced with 3 equivalents of hydrogen at 25 p.s.i.g. in the presence of palladium on charcoal in absolute ethanol. The resulting mixture is filtered and the filtrate concentrated *in vacuo* to a residue which is refluxed 1 hour with a solution of 12.3 g. of silver nitrate in 100 ml. of 0.5M aqueous ammonia. The resulting mixture is filtered; the filtrate is acidified with glacial acetic acid and the precipitate is reprecipitated from concentrated 6*M* aqueous ammonia on addition of glacial acetic acid, to provide 6-methylsulfonyl-2-keto-(1H)-quinoxaline, m.p. 347—350°C.

EXAMPLE 7.

Preparation of 7-methoxy-2-keto-(1H)-quinoxaline

2-Nitro-4-methoxy aniline (84 g., 0.50 mole) and xylene (25 ml.) are heated in a flask to 130°C. The magnetically stirred molten mixture is treated with solid bromoacetic acid (34.8 g., 0 25 mole) in portions at a reaction temperature of 130°C. for 2 hours. The thick mixture is heated for 0.5 hours longer, cooled to 0°C. and treated with 80 ml. of 20 wt. % aqueous ammonia, and the resulting solution is filtered. The filtrate is acidified with concentrated hydrochloric acid to precipitate crude 4-methoxy-2-nitroanilinoacetic acid, m.p. 165—166°C., which is dissolved in 122 ml. of ethanol and subjected to reduction with 73 g. of tin and 162 ml. of concentrated HCl. Following precipitation of tin with H_2S and filtration, a clear solution is obtained which yields a grey precipitate of 7-methoxy-3,4-dihydro-2-keto(1H)-quinoxaline, which melts at 181—184°C. after recrystallization from absolute ethanol.

Oxidation of the above product (11.5 g.) with 13 ml. 30% hydrogen peroxide in 145 ml. 8 wt.% sodium hydroxide for 2 hours at 90°C., followed by filtration and acidification with glacial acetic acid, gives 7-methoxy-2-keto-(1H)-quinoxaline, m.p. 237—239°C.

Following the procedure exactly as described in Example 7 except that the 2-nitro-4-methoxyaniline of Example 7 is replaced with equivalent amounts of 2-nitro-5-methoxyaniline and 2-nitro-5-chloroaniline, respectively, there are

obtained 6-methoxy-2-keto-(1H)-quinoxaline and 6-chloro-2-keto-(1H)-quinoxaline, respectively.

EXAMPLE 8.

Preparation of 6-nitro-2-keto-(1H)-quinoxaline

To finely powdered 2-keto-(1H)-quinoxaline (25.0 g., 0.171 mole) is added 250 ml. concentrated sulfuric acid with cooling and stirring at below 24°C. The resulting stirred suspension is cooled to 10°C. and treated with 17.5 g. of powdered potassium nitrate. After 5 minutes the mixture is warmed to 43°C. After 15 minutes the mixture is poured into stirred ice water to give crude 6-nitro-2-keto-(1H)-quinoxaline which, after digestion with 20 g. sodium bicarbonate in 200 ml. water at 90°C., melts at 287—289°C.

EXAMPLE 9.

Preparation of 6-bromo-2-keto-(1H)-quinoxaline

To a stirred solution of 2-keto-(1H)-quinoxaline (14.6 g., 0.1 mole) and silver sulfate (15.6 g., 0.05 mole) in 100 ml concentrated sulfuric acid at 20°C. is added 5.2 ml. liquid bromine. The mixture is stirred for 24 hours at room temperature, heated to 50°C. and filtered. The deep-red filtrate is poured on 650 g. of vigorously stirred crushed ice and the precipitate is collected and washed with water and recrystallized twice from boiling glacial acetic acid, to provide 6-bromo-2-keto-(1H)-quinoxaline, m.p. 298—300°C.

EXAMPLE 10.

Preparation of 2,3-dihydroxy-6-trifluoromethyl-quinoxaline

3-Nitro-4-amino-trifluoromethylbenzene (20.6 g., 0.100 mole) is hydrogenated in absolute ethanol in the presence of palladium on charcoal at 15—40 p.s.i.g. of hydrogen to give a solution of 4-(trifluoromethyl)-*o*-phenylenediamine, which is filtered and treated with 150 ml. diethyl oxalate at reflux with removal of ethanol. The resulting precipitate of 2,3-dihydroxy-6-trifluoromethyl-quinoxaline has a melting point of 342—343°C. after filtration and washing with ether.

Where in Example 10 the 4-(trifluoromethyl)-*o*-phenylenediamine of Example 10 is replaced by equivalent amounts of N-methyl-*o*-phenylenediamine, 4-cyano-*o*-phenylenediamine and 4-chloro-*o*-phenylenediamine, respectively, there are obtained 4-methyl-2, 3-diketo-(1H)-quinoxaline, 6-cyano-2,3-dihydroxy-quinoxaline and 6-chloro-2,3-dihydroxy-quinoxaline. When these compounds are subjected to the chlorination procedure of Example 11 (below) 2-chloro-3-keto-4-methyl-quinoxaline (m.p. 129—130°C.), 2,3-dichloro-6-cyanoquinoxaline and 2,3,6-trichloroquinoxaline, respectively, are produced.

EXAMPLE 11.

Preparation of 2,3-dichloro-6-(trifluoromethyl)-quinoxaline

Reaction of 2,3-dihydroxy-6-trifluoromethylquinoxaline (m.p. 342—343°C.) with 150 ml. of phosphorus oxychloride and 2 ml. N,N-dimethylformamide at reflux, followed by concentration *in vacuo* and quenching on ice gives 2,3-dichloro-6-(trifluoromethyl)-quinoxaline, m.p. 81.5—82.5°C., after recrystallization from *n*-butylchloride.

Following the procedure of Example 11 except that the 2,3-dihydroxy(or diketo)-4-trifluoromethylquinoxaline of Example 11 is replaced by an equivalent amount of 2,3-dihydroxy-6-methylthioquinoxaline, 2,3-dihydroxy-6-methylsulfonylquinoxaline, 8-fluoro-2-keto-(1H)-quinoxaline (from Example 4), 6-trifluoromethyl-2-keto(1H)-quinoxaline (from Example 4), 6-methylsulfonyl-2-keto(1H)-quinoxaline (from Example 6), 6-fluoro-2-keto-(1H)-quinoxaline (from Example 5), 6-cyano-2-keto-(1H)-quinoxaline (from Example 5,) 6,7-dichloro-2-keto-(1H)-quinoxaline (from Example 4), 6-bromo-2-keto-(1H)-quinoxaline (from Example 9), 6-methoxy-2-keto(1H)-quinoxaline (from Example 7), 6-hydroxy-2-keto-(1H)-quinoxaline (from Example 5), 5-chloro-2-keto-(1H)-quinoxaline (from Example 4), 5-nitro-2-keto-(1H)-quinoxaline (from Example 4), 7-chloro-5-nitro-2-keto-(1H)-quinoxaline (from Example 4), 7-chloro-5-nitro-3-keto-(4H)-quinoxaline (from Example 4), 6-chloro-2-keto-(1H)-3-ethoxyquinoxaline, 3-acetyl-2-keto-(1H)-quinoxaline, and 6-chloro-2-keto-(1H)-quinoxaline, respectively, there are obtained 2,3-dichloro-6-methylthioquinoxaline (m.p. 138.5—139°C.); 2,3-dichloro-6-methylsulfonylquinoxaline (170—172°C.); 2-chloro-8-fluoroquinoxaline (m.p. 112—113°C.); 2-chloro-6-trifluoromethyl-quinoxaline (m.p. 118—120°C.); 2-chloro-6-methylsulfonylquinoxaline 2-chloro-6-

fluoroquinoxaline (m.p. 129—132°C.); 2-chloro-6-cyanoquinoxaline; 2,6,7-trichloroquinoxaline (m.p. 147—148°C.); 2-chloro-6-bromoquinoxaline; 2-chloro-6-methoxyquinoxaline; 2-chloro-6-hydroxyquinoxaline (m.p. 254°C.); 2,5-dichloroquinoxaline (m.p. 132—135°C.); 2-chloro-5-nitroquinoxaline; 2,7-dichloro-5-nitroquinoxaline; 3,7-dichloro-5-nitroquinoxaline; 2,6-dichloro-3-ethoxyquinoxaline (m.p. 57—62°C.); 2-chloro-3-acetyl quinoxaline, and 2,6-dichloroquinoxaline, respectively.

EXAMPLE 12.

Preparation of 6-(trifluoromethyl)-3-phenylthio-2-chloroquinoxaline

2,3-Dichloro-6-(trifluoromethyl)-quinoxaline, (2.67 g., 0.010 mole) is treated with a solution of freshly distilled thiphenol (1.04 ml., 0.0101 mole) and 1,8-*bis*-(dimethylamino)-naphthalene (2.15 g., 0.0101 mole) in dry acetonitrile at 25°C. under N_2 for 1.5 hour. The resulting mixture is concentrated *in vacuo*, the residue boiled with 40 ml. hexane, the mixture filtered and the filtrate cooled to give white needles of 6-(trifluoromethyl)-3-phenylthio-2-chloroquinoxaline, m.p. 102—105°C.

As in Example 12, when the 2,3-dichloro-6(trifluoromethyl)-quinoxaline of Example 12 is replaced by equivalent amount of the 2,3,6-trichloroquinoxaline of Example 10 there is obtained 2,6-dichloro-3-phenylthioquinoxaline (m.p. 92—98°C.).

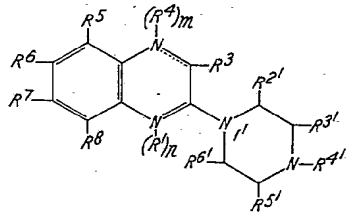
EXAMPLE 13.

Preparation of 2-chloro-5-fluoroquinoxaline

A mixture of 5-fluoro-2-keto-(1H)-quinoxaline (1.21 g., from Example 5), phosphorus pentachloride (1.2 g.) and phosphorus oxychloride is heated 45 minutes with stirring at 85° under N_2 and concentrated *in vacuo*, and the residue is slurried in ether and poured on crushed ice. The ethereal layer is separated, dried under Na_2SO_4, and concentrated, and the residue is sublimed to give white crystals of 2-chloro-5-fluoroquinoxaline, m.p. 88—89°C.

WHAT WE CLAIM IS:—

1. A compound of the formula:



in which the dotted line indicates that the compounds are saturated or ethylenically unsaturated at the 3,4-position; R^1 is oxygen; each of *n* and *m* is 0 or 1; R^4 is oxygen, hydrogen, alkyl, or aminoalkyl and R^3 is hydrogen, alkyl, alkoxycarbonyl, alkanoyl, aryl, substituted aryl, alkylthio, arylthio, alkoxy, amino, keto, alkylamino, dialkylamino, hydroxy, halo, carboxy, carbamoyl, N-alkylcarbamoyl, N,N-dialkylcarbamoyl or alkylimino; or R^4 and R^3 are joined to form, together with the adjacent nitrogen and carbon atoms of the quinoxaline nucleus, a 5-to-7-membered ring; each of R^5, R^6, R^7 and R^8 is hydrogen, allyl, haloalkyl, haloalkylthio, arylalkyl, cycloalkyl, aroyl, alkyl, nitro, alkanoyl, aryl, substituted aryl, alkylthio, alkylsulfonyl, haloalkylsulfonyl, alkylsulfinyl, haloalkylsulfinyl, arylthio, alkoxy, haloalkoxy, amino, alkylamino, dialkylamino, hydroxy, halo, carboxy, alkoxycarbamoyl, N-alkylcarbamoyl, cyano, N,N-dialkylcarbamoyl or dialkylsulfamoyl; $R^{4'}$ is hydrogen, allyl, substituted allyl, haloalkyl, arylalkyl, cycloalkyl, alkanoyl, aroyl, alkylidenaminoxycarbonyl, alkoxycarbonylalkylenedithiocarbonyl, alkyldithiocarbonyl, β-cyanoethyl, alkoxycarbonyl, aryloxycarbonyl, or aralkyloxycarbonyl; and each of $R^{2'}$, $R^{3'}$, $R^{5'}$ and $R^{6'}$ is keto or two of the following univalent atoms or groups: hydrogen, alkyl, alkanoyl, aryl, substituted aryl, carboxy, alkoxycarbonyl, carbamoyl, N-alkylcarbamoyl or N,N-dialkylcarbamoyl, or $R^{2'}$ and $R^{3'}$ and/or $R^{5'}$ and $R^{6'}$ are joined to form a cycloaliphatic substituent sharing the 2',3'-carbon atoms and/or 5',6'-carbon atoms, as the case may be, of the piperazine ring or a non-toxic, pharmaceutically acceptable acid-addition salt thereof.

2. A compound according to Claim 1 in which
n is 0;
R^4 is hydrogen or alkyl;
R^3 is hydrogen, hydroxyl, alkoxy, aryloxy, nitro, keto, amino, dialkylamino, alkanoyl, carboxyl, or halo;
R^5, R^6, R^7 and R^8 are hydrogen, halogen, alkoxy, hydroxy, dialkylsulfamoyl, haloalkylthio, haloalkylsulfinyl, haloalkylsulfonyl, haloalkoxy, cyano, alkyl, nitro, trifluoromethyl, or haloalkyl;
$R^{4'}$ is hydrogen, benzyl, allyl, acetoacetyl, alkoxycarbonyl, alkylidenaminoxycarbonyl, carboalkoxyalkylenedithiocarbonyl, or alkyldithiocarbonyl;
$R^{2'}$, $R^{3'}$, $R^{5'}$ and $R^{6'}$ are hydrogen, keto, or alkyl; or
$R^{2'}$ and $R^{3'}$; and/or $R^{5'}$ and $R^{6'}$ are joined, together with the carbon atoms to which they are attached, to form a cycloaliphatic substituent.

3. A compound according to Claim 2 in which
R^3 is hydrogen or hydroxyl (or keto, in which case R^4 is hydrogen);
R^5 and R^8 are hydrogen, fluorine, bromine, chlorine, hydroxyl, C_{1-5} alkoxy or di(C_{1-5} alkyl)sulfamoyl;
R^6 is hydrogen, fluorine, bromine, chlorine, cyano, nitro, or trifluoromethyl;
$R^{3'}$ and $R^{5'}$ are hydrogen or keto; $R^{6'}$, R^7 and $R^{2'}$ are hydrogen; $R^{4'}$ is hydrogen, or alkylidenaminoxycarbonyl having from 2 to 6 carbon atoms, and *n* is 0.

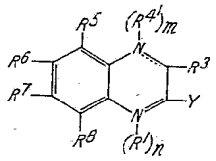
4. 6-Chloro-2-(1'-piperazinyl)-quinoxaline.

5. 6-Cyano-2-(1'-piperazinyl)-quinoxaline.

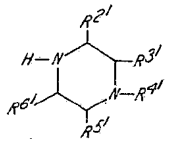
6. 6-Trifluoromethyl-2-(1'-piperazinyl)-quinoxaline.

7. 3-Keto-(4H)-2-(1'-piperazinyl)-quinoxaline.

8. A process for preparing a compound as claimed in Claim 1 which comprises reacting a quinoxaline having the structure:



with a piperazine having the formula:



in which Y is a replaceable group and the dotted line, R^1, R^3, R^4, R^5, R^6, R^7, R^8, $R^{2'}$, $R^{3'}$, $R^{4'}$, $R^{5'}$, $R^{6'}$, *m* and *n* are as defined in Claim 1.

9. A process as claimed in Claim 8 in which Y is halogen, mercapto, trialkylammonium, tosyloxy, mesyloxy, trimethylsilyloxy, alkoxy, amino, alkylamino or alkylthio.

10. A process as claimed in Claim 8 or 9 in which *n*, R^3, R^4, R^5, R^6, R^7, R^8, $R^{2'}$, $R^{3'}$, $R^{4'}$, $R^{5'}$ and $R^{6'}$ are as defined in Claim 2.

11. A process as claimed in Claim 10 in which R^3, R^5, R^6, R^7, R^8, $R^{2'}$, $R^{3'}$, $R^{4'}$, $R^{5'}$ and $R^{6'}$ are as defined in Claim 3.

12. A pharmaceutical composition containing a compound as claimed in any one of Claims 1 to 7 and a pharmaceutical carrier.

13. A composition as claimed in Claim 12 in the form of a tablet, pill, capsule, powder, granules, sterile parenteral solution, or suspension.

14. A composition as claimed in Claim 12 in the form of a tablet or pill comprising an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former and the two components being separated by an enteric layer.

15. A composition as claimed in Claim 12 in the form of a syrup, elixir, aqueous or oily suspension, or flavoured emulsion with an edible oil.

16. A process for producing a compound as claimed in Claim 1, substantially as hereinbefore described in any one of Examples 1 to 3.

17. A compound as claimed in Claim 1, when prepared by a process as claimed in any one of Claims 8 to 11 and 16.

18. A composition as claimed in any one of Claims 12 to 15, in which the said compound is a compound as claimed in Claim 17.

For the Applicants,
D. YOUNG & CO.,
Chartered Patent Agents,
9 & 10 Staple Inn,
London WC1V 7RD.

Printed for Her Majesty's Stationery Office by the Courier Press, Leamington Spa, 1976.
Published by the Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from which copies may be obtained.